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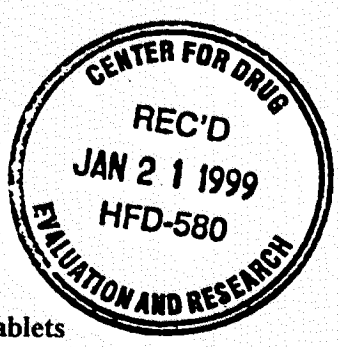
NEW CORRESP

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

January 20, 1999

Via Fax to D Moore

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Subject: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens A) Tablets 0.3 mg, 0.625 mg and 0.9 mg**

Re: **Telephone Conference Call of January 22, 1999**

Dear Dr. Rarick:

We appreciate the opportunity to discuss with you and your staff two (2) remaining review issues: the approval of a 0.3 mg dosage strength and the wording to be used in the labeling to describe the delayed-release characteristics of Cenestin. To focus our discussion, we offer the following discussion points.

0.3 mg Dosage Strength

During our June 19, 1997 pre-IND meeting we discussed the study design which featured dose titration in reflection of clinical practice. Dr. Heidi Jolson stated that she would like to see the titration start at 0.3 mg. After the formal meeting, Ken Phelps discussed with Dr. Rarick the difficulty of starting at 0.3 mg. Dr. Rarick agreed and said not to include the 0.3 mg – saying that it 'could be handled in labeling'. However, in the spirit of cooperation and an attempt design a protocol modeled on actual clinical practice, we submitted for consideration a study design that included the possibility of lowering the dose from a starting dose of 0.625 mg. In subsequent telephone discussions with the Division regarding the merits of the submitted protocol it was agreed by all parties that efficacy evaluation would be not be broken down by dose. This approach to the analysis of efficacy was confirmed in our pre-NDA meeting on January 27, 1997 at which we were requested to present only a table showing number of patients per dosage treatment.

We now understand that since only two patients were exposed to the 0.3 mg dose during the clinical study, and that no in vivo bioavailability data are available on this strength that a preliminary decision has been made to exclude this strength from approval. We request a re-consideration of this decision based on discussion presented above and the following points in support of our position that the 0.3 mg strength should be approved along with the 0.625- and 0.9 mg dosage strengths.

- It is *a priori* impossible to predict the effective dose for any given patient. The target patient population for the 0.3 mg dose is low – in the Kaiser Health Plan, 4.6% of patients aged <55

- It is *a priori* impossible to predict the effective dose for any given patient. The target patient population for the 0.3 mg dose is low – in the Kaiser Health Plan, 4.6% of patients aged <55 years using ERT are successfully maintained at 0.3 mg (private communication Dr. B. Ettinger). Given that our proposed labeling, in accord with past and draft short-acting oral estrogen class labeling, indicated to start at 0.625 mg and increase or reduce the dose to the lowest effective dose, not approving a 0.3 mg dose compromises treatment options for the physician/patient.
- It has been shown in other studies of estrogens that the control of vasomotor symptoms is achieved in a dose-related manner. For example, in a study cited in our NDA, Mortola, et. al. showed a dose-related response to Estratab (esterified estrogens , USP) at 0.3-, 0.625- and 1.25 mg in the reduction of hot flashes compared to a placebo.
- The Cenestin 0.3 mg dosage is exactly proportional to the 0.625 mg dose, in the same manner as the 0.9 mg is proportional to the 0.625 mg dose; the only difference between these three strengths is the amount of lactose filler which compensates for the difference in synthetic conjugated estrogens. In our amendments of December 8 and 15, 1998 we submitted comparative dissolution data for all three strengths, which we believe satisfy the waiver criteria as outlined in 21 CFR 320.22.
- The DESI review concluded that doses of 0.3-1.25 of estrogens were required to treat senile vaginitis, kraurosis vulvae and pruritus vulvae, while doses in the range of 0.3-2.5 mg were required to treat the menopausal syndrome. Thus, other estrogen products have been granted the vasomotor symptom treatment indication for the entire range of dosage strengths based on a showing of bioequivalence of only a single strength (ANDA approvals are based on a policy of one high dosage strength study covering up to three (3) additional proportionally formulated dosage strengths).

Labeling Nomenclature - Release characteristics

Our proposed labeling included the sentence "The Cenestin formulation is designed to slowly release the synthetic conjugated estrogens over a period of several hours". Per a Division letter of December 14, 1998, it was requested, without explanation, that this sentence be deleted. In our December 15 amendment we offered the following explanation for why we did not incorporate this suggested change into the draft labeling.

> "The development goal was a product that delayed the release of the drug substance from the tablet matrix. Cenestin is not an immediate release product and this fact is reflected in the proposed dissolution specifications. We welcome discussion with the reviewer on revised wording that maintains this essential release characteristic."

We understand now that the Division wishes to maintain its position that the subject sentence be deleted. We offer the following points for reconsideration on this issue.

- Modified release dosage forms are discussed in the current USP and are divided into two (2) types - a delayed release (such as enteric-coated products) and extended release. While we do not believe our product to be an extended release product, it is, however, designed using a coating to slowly dissolve. That the product is not an immediate release tablet is illustrated by the eight (8) hour dissolution testing specification.
- We believe that the labeling should accurately describe this oral dosage form. This information is particularly useful to poison control centers, which provide treatment advice in acute or overdose situations.
- The FDA determined in 1986 (55 Fed Reg 5074-8, February 13, 1990) that Premarin® tablets were a modified release dosage form. This reference is being made to illustrate the classification

that was made to a tablet that has similar *in vitro* bioavailability and *in vivo* dissolution profiles as Cenestin. Indeed, in the Division's minutes of the June 19 1997 pre-IND meeting, the biopharmaceutics comments described the proposed product as having "modified drug releasing characteristics"

- We are not insisting on any particular wording to describe the release phenomenon. Perhaps we can combine the information from the subject sentence and the sentence that follows it [Cenestin maximum plasma concentrations of the conjugated and unconjugated estrogens are attained within 4 to 10 hours after dose administration] to yield:

  The Cenestin formulation is designed to slowly release conjugated estrogens to achieve maximum plasma concentrations of conjugated and unconjugated estrogens 4 to 10 hours after oral administration.

We appreciate the opportunity to discuss these issues with you on Friday, January 22, 1999 at 9:00 a.m. Should you have any questions about the discussion points above, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213

(513) 731-9900

ORIG AMENDMENT

February 2, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens A Tablets) 0.3 mg, 0.625 mg and 0.9 mg**

Re: **Labeling Amendment**

Dear Dr. Rarick:

Reference is made to a letter from Lana Pauls, M.P.H., dated December 14, 1998 requesting information to continue the review of NDA 20-992 for Cenestin™ Tablets. In response to this letter, we submitted an amendment on December 15, 1998, which included, among other items, revisions to the labeling (physician and patient package inserts). On February 1, 1999, Ms. Diane Moore called to inform of us of several changes to the labeling and to request submission of revised container and carton labels. This amendment contains revised labeling and container and carton labels.

This **Amendment** is submitted in 1 volume and includes three (3) copies, an archival copy and two review copies. Please note that one copy each of the 'marked-up' and 'clean' version of the draft package inserts is included each copy. In addition, a desk copy to Ms. Diane Moore is provided.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

KPhelps for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h
cc: Desk copy to Diane Moore

CENTER FOR DRUG EVALUATION AND RESEARCH
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HFD-580

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

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February 4, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens A Tablets) 0.3 mg, 0.625 mg and 0.9 mg**

Re: **Labeling Amendment**

Dear Dr. Rarick:

Reference is made to telephone call of today, February 4, 1999 between Duramed and members of the Division of Reproductive and Urological Drug Products and Division of Pharmaceutical Evaluation II. In this telephone call, agreement was reached on changes to two sentences in the physician insert under the Pharmacokinetics/Absorption section.

This **Amendment** is submitted in 1 volume and includes three (3) copies, an archival copy and two review copies. Please note that one copy of the 'marked-up' impacted page from the draft physician insert and a 'clean' version of both the physician and patient package inserts are included each copy. In addition, a desk copy to Ms. Diane Moore is provided. A diskette containing the MS Word and Adobe PDF image of the labeling is provided in the archive and Ms. Moore's copy.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h
cc: Desk copy to Diane Moore

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ORIG AMENDMENT

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

The Art of Leadership...
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February 10, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-992: Cenestin™ (Synthetic Conjugated Estrogens A Tablets) 0.625 mg and 0.9 mg**

Re: **Chemistry Amendment**

Dear Dr. Rarick:

Reference is made to telephone conference call on February 4, 1999 between Duramed and Drs. Rhee and Lin and Ms. D. Moore. In this conference call, Dr. Rhee requested the following information:

- Methods validation reports for the content uniformity and dissolution methods.
- Correct 'typical' chromatograms for drug substance and drug product assay methods.
- Correction of an apparent discrepancy of the normality of the phosphate buffer in the mobile phase between that presented in the dissolution method and its validation report.
- Updated stability specifications.

In this **Chemistry Amendment** we reply to Dr. Rhee's request. The dissolution method has been updated and re-validated to include the quantitation of sodium equilin sulfate. The improved method and validation report are attached. The content uniformity method is unchanged, only the presentation of results are updated to include sodium 17α-dihydroequilin in the assay sum; the content uniformity method had been previously validated for this analyte. For reviewers convenience, the content uniformity method and the validation information previously submitted have been included in this amendment.

REVIEWS COMPLETED

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Annotated typical chromatograms for the drug substance and drug product assays are included.

Updated specifications for drug substance, in-process and release testing were included in our December 15, 1998 amendment in response to the Division's December 14, 1998 Information Request letter. Updated stability specifications are included in today's amendment.

This **Amendment** is submitted in 1 volume and includes three (3) copies, an archival copy and two review copies.

If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h
cc: Desk copy to Diane Moore

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

March 1, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens, A Tablets) 0.625 mg and 0.9 mg**

Re: **Labeling Amendment**

Dear Dr. Rarick:

Reference is made to telephone call of today, March 1, 1999 between Mr. John Rapoza and Mr. Ken Phelps of Duramed, and Ms. Diane Moore and Dr. David Lin of the Division of Reproductive and Urological Drug Products. In this telephone conference call, agreement was reached on changes to drug product labels, cartons and inserts.

This **Amendment** is submitted in one (1) volume and includes three (3) copies, an archival copy and two review copies. One copy of the labeling is contained in each volume. In addition, a desk copy to Ms. Diane Moore is provided. A diskette containing the MS Word and Adobe PDF image of the labeling is provided in the archive and Ms. Moore's copy.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h
cc: Desk copy to Diane Moore

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ORIG AMENDMENT

SV

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

March 4, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens, A Tablets) 0.625 mg and 0.9 mg**

Re: **Clinical Amendment – Safety Update**

Dear Dr. Rarick;

Reference is made to telephone call of today, March 4, 1999 between Mr. Ken Phelps of Duramed, and Ms. Diane Moore of the Division of Reproductive and Urological Drug Products. In this telephone conference call, we were requested to provide a safety update.

We hereby state that since the filing of the subject NDA, we have had no further contact with any of the patients in the pivotal clinical trial. Furthermore, we have conducted no other clinical studies in humans. Therefore, we report that there are no adverse events of human experience to report in this safety update.

This **Amendment** is submitted in one (1) volume and includes two (2) copies, an archival copy and one review copy. In addition, a copy is being faxed to Ms. Diane Moore.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h

REVIEWS COMPLETED

CSO ACTION:
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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

March 15, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-992 Cenestin™ (synthetic conjugated estrogens, A) Tablets 0.625 mg and 0.9 mg**

Re: **Labeling, Pharmacology and CMC Amendment**

Dear Dr. Rarick:

Reference is made to telephone call of today, March 15, 1999 between Mr. John Rapoza and Mr. Ken Phelps of Duramed, and Dr. Lisa Rarick, Ms. Diane Moore and other members of the Division of Reproductive and Urological Drug Products. In this telephone conference call, agreement was reached on three topics:

1. References to the literature which formed the basis of the pharmacology review would be submitted to the NDA.
2. Several minor changes to the drug product labeling were identified. In addition, the following significant changes would be incorporated:
   -
   - change of the established name from (synthetic conjugated estrogens, A tablets) to (synthetic conjugated estrogens, A) tablets.
3. Revised dissolution specifications.

In this **Amendment** we are furnishing the pharmacology literature references, revised physician and patient inserts, container and carton labels and revised finished product and stability specifications reflecting the new dissolution specifications.

This **Amendment** is submitted in one (1) volume and includes four (4) copies, an archival copy and three review copies. In addition, a desk copy to Ms. Diane Moore is provided. Two (2) copies of the labeling are contained in each volume, one marked-up copy indicating changes made since the last amendment and a second, clean copy. A diskette containing the

MS Word and Adobe PDF image of the labeling is provided in both the archive and Ms. Moore's copy.

As required by 21 CFR 314.94(d)(5), Duramed Pharmaceuticals, Inc. is forwarding today a true copy of the amendment, including a completed copy of FDA Form 356h to the Cincinnati District Office. Duramed certifies that the information contained in the "field copy" is the same as that submitted to FDA headquarters. The field copy is contained in one (1) volume.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h
cc: Desk copy to Diane Moore

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

March 17, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-992 Cenestin™ (synthetic conjugated estrogens, A) Tablets 0.625 mg and 0.9 mg**

Re: **Labeling and CMC Amendment**

Dear Dr. Rarick:

Reference is made to telephone call of today, March 17, 1999 between Mr. Ken Phelps of Duramed, and Ms. Diane Moore and Dr. David Lin of the Division of Reproductive and Urological Drug Products. Reference is also made to an amendment dated March 15 which contained Labeling, Pharmacology and CMC information. In today's telephone conference call, agreement was reached on two topics:

1. The dissolution specifications discussed on March 15 for the equilin analyte at the 2 hour time point were , as we had recorded. Thus, the March 15 amendment contained a finished product specification and stability specification that is in error.
2. Ms. Moore identified a typographical error in the Indications section of the insert. This error is corrected in the attached labeling.

In this **Amendment** we provide the revised physician and patient inserts and revised finished product and stability specifications reflecting the corrected dissolution specifications.

This **Amendment** is submitted in one (1) volume and includes three (3) copies, an archival copy and two review copies. In addition, a desk copy to Ms. Diane Moore is provided. A diskette containing the MS Word and Adobe PDF image of the labeling is provided in both the archive and Ms. Moore's copy.

As required by 21 CFR 314.94(d)(5), Duramed Pharmaceuticals, Inc. is forwarding a true copy of the amendment, including a completed copy of FDA Form 356h to the Cincinnati

District Office. Duramed certifies that the information contained in the "field copy" is the same as that submitted to FDA headquarters. The field copy is contained in one (1) volume.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h
cc: Desk copy to Diane Moore